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THE ONES TO WATCH

A PHARMA MATTERS REPORT.

OCTOBER-DECEMBER 2009

Expert review from Thomson Reuters of the most promising drugs changing clinical phase, receiving approval and launched this quarter, based on the strategic data and insight of *Thomson Pharma*[®], the world's leading pharmaceutical competitive intelligence solution.



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This edition of *The Ones to Watch* contains several examples showing how granting of orphan drug status has enabled pharmaceutical innovators to bring help to sufferers of rare diseases. In fact, a January 2010 report by the Tufts Center for the Study of Drug Development found that the number of drugs receiving orphan status has doubled since 2000.

As we see from this quarter's selection, drugs for small patient populations such as Dyax's Kalbitor for hereditary angioedema, and Allos and Celgene's treatments for T-cell lymphomas have already reached the market. Meanwhile drugs for urea cycle disorder and multiple myeloma are moving apace through the pipeline, giving hope to patients with diseases that are unlikely to ever deliver a blockbuster drug. And as big pharma continues to move away from chasing blockbusters, they will likely be rewarded by a growing orphan drugs market, expected to increase to US\$81.8 billion in 2011 from US\$58.7 billion in 2006, according to BCC Research.

Unsurprisingly, drugs for cancer continue to attract considerable attention, with 25% of this quarter's promising drugs being for oncological indications. And companies are looking at the lifestyle factors that can lead to cancer, with potential treatments for addictions also making waves. Alkermes is aiming to treat alcohol addiction with ALKS-33 now beginning phase II trials. And nicotine addiction is the subject of Nabi Biopharmaceuticals' NicVAX, which began the first of two phase III trials in November.

Let's take a closer look at the five most promising drugs launched or receiving approval, and moving through each of the clinical phases, between October and December 2009.

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THE FIVE MOST PROMISING DRUGS LAUNCHED OR RECEIVING APPROVAL

| DRUG | DISEASE | COMPANY |
|---------------------|---------------------------------------|--------------------------------|
| Kalbitor® | Hereditary angioedema | Dyax |
| Onbrez® Breezhaler® | Chronic obstructive pulmonary disease | Novartis |
| Folotyn™ | Peripheral T-cell lymphoma | Allos |
| Istodax® | Cutaneous T-cell lymphoma | Celgene |
| Vibativ™ | Gram positive bacterial infection | Theravance and Astellas Pharma |

We kick off this edition of *The Ones to Watch* with a treatment for hereditary angioedema (HAE), a disease characterized by sudden episodes of acute inflammation of the face, extremities, abdomen and airways. The disease affects between 1 in 10,000 and 1 in 50,000 people, and is caused by low levels of C1 esterase inhibitor, which inhibits the peptidase kallikrein, a key mediator of inflammation.

Kalbitor® (ecallantide), a recombinant peptide inhibitor of kallikrein developed by Dyax, is delivered subcutaneously for convenient self-administration at the onset of an HAE attack. Data from the phase III EDEMA3 and EDEMA4 studies showed significant improvement of the severity of HAE attacks compared to placebo.

The drug has had orphan status in the US and Europe since 2003. After priority review, the FDA approved the drug in December 2009 for acute attacks of HAE in patients older than 16 years and Dyax launched the drug in the US in February 2010. Dyax is also collaborating with Cubist Pharmaceuticals to develop the drug as a way of preventing blood loss during coronary artery bypass surgery. Thomson Pharma forecasts sales of US\$150 million in 2013.

Next up is **Onbrez® Breezhaler®**, a once-daily formulation of indacaterol for the maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD). Approved in the EU in December 2009 and launched in Germany later that month, it represents the first new inhaled compound for COPD patients in the EU in seven years.

Developed by Novartis, the Onbrez Breezhaler comprises indacaterol - a long-acting beta-2 agonist and bronchodilator - delivered by SkyePharma's SkyeHaler multidose dry-powder inhaler at doses of 150 and 300mg. The phase III INVOLVE, INHANCE and INLIGHT trials have shown the drug can act within five minutes to improve lung function and breathing compared with treatment standard, Boehringer Ingelheim and Pfizer's Spiriva® (tiotropium). Patients using the Onbrez

Breezhaler did not need relief medication on 20% more days than those using Spiriva.

The drug is awaiting launch in the US, pending ongoing discussions with the FDA, while Novartis is also developing the drug for asthma. Thomson Pharma forecasts sales of US\$397 million in 2013.

Folotyn™ is an intravenous formulation of pralatrexate for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL). The disease has a poor prognosis with patients almost always relapsing or developing resistance to initial therapy. Pralatrexate is an antifolate which kills rapidly dividing cells.

Developed by Allos under license from the **Memorial Sloan-Kettering Cancer Center** and **SRI International**, Folotyn was granted accelerated approval by the FDA in September 2009. It is the first and only FDA-approved drug for relapsed or refractory PTCL, and was launched in October 2009. While improvement in progression-free or overall survival has not been proved, the FDA review found that the drug is likely to provide clinical benefit to patients. Allos believes the trial on which the approval was based, PROPEL, was the largest international multicenter trial ever conducted of relapsed or refractory PTCL patients. 27% of patients on the course of weekly injections of Folotyn for six weeks in seven week cycles responded to treatment.

Meanwhile, Folotyn is also being investigated for its use in treating bladder cancer, lymphoproliferative malignancies, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma (CTCL) and solid tumors. As part of the accelerated approval process Allos will conduct additional trials of Folotyn in PTCL patients.

Staying with T-cell lymphoma, another newly approved drug is the histone deacetylase inhibitor **Istodax®** (romidepsin) for the treatment of CTCL in patients who have already received one systemic therapy. The drug, developed by Celgene after its acquisition of Gloucester Pharmaceuticals, and delivered as an intravenous infusion, received US approval in November 2009 after five years in the Fast Track program.

Patients with CTCL who fail initial treatment have few treatment options meaning Istodax, which has orphan designation in both the US and Europe, meets a significant unmet need. The FDA approval was supported by two trials in which patients were given Istodax three times a month, with over a third of patients responding to treatment. The drug is the second anticancer histone deacetylase inhibitor to be approved after Merck's Zolinza, also for refractory CTCL, suggesting significant potential in this class of compounds.

Our final newly approved or launched drug is **Vibativ™** (telavancin), launched in the US in November 2009 to treat complicated skin and skin structure infections caused by Gram positive bacteria after phase III trials showed the drug's non-inferiority relative to the standard of care vancomycin. Health Canada approved Vibativ for the same indication in October 2009, and the drug is also being developed for hospital-acquired pneumonia.

Developed by Theravance and Astellas, the lipoglycopeptide antibiotic is administered as a once-daily injection and works by inhibiting peptidoglycan synthesis in the formation of the thick cell wall in Gram positive bacteria. Thomson Pharma forecasts sales of US\$128.2 million in 2013.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE III TRIALS

| DRUG | DISEASE | COMPANY |
|-------------|------------------------------|--|
| GRASPA® | Acute lymphoblastic leukemia | ERYtech |
| HPN-100 | Urea cycle disorders | Hyperion Therapeutics |
| necitumumab | Non-small cell lung cancer | ImClone |
| NicVAX™ | Nicotine addiction | Nabi Biopharmaceuticals |
| tivozanib | Solid tumors | AVEO Pharmaceuticals/ Kyowa Hakko Kirin |

Side effects of L-asparaginase, a critical component of acute lymphoblastic leukemia (ALL) treatment, include severe allergic reaction and problems with blood coagulation, leading to bleeding. The drug works by depleting the amino acid asparagine in the blood plasma, thereby starving leukemia cells unable to make their own asparagine.

ERYtech is hoping that by encapsulating L-asparaginase in patients' erythrocytes in a formulation it has named **GRASPA®**, the drug will become more effective while decreasing side effects, as seen in encouraging phase II trials completed in 2008. Phase III trials of GRASPA began in France in November 2009 in patients with relapsed ALL. ERYtech claims the encapsulated formulations increases the half life of L-asparaginase from 1 to 30 days, and the new formulation could see doses reduced by 100-fold. The drug has orphan status in the US and EU for this indication.

ERYtech is also investigating the drug's potential to treat other solid tumors, and initiated a French phase I trial for pancreatic cancer in December 2009.

Urea cycle disorders (UCD), genetic diseases in which an enzyme deficiency allows ammonia to build up in the bloodstream and can cause brain damage, coma and death, affect one in 10,000 births. As well as dietary control, the main medication is the 'ammonia scavenger' Buphenyl™.

Hyperion Therapeutics, under license from Ucyclyd Pharma, is developing an ammonia scavenging alternative, **HPN-100** (glycerol phenylbutyrate), an oral liquid formulation of a prodrug of Buphenyl's active ingredient. A phase III trial of HPN-100 began in the US in October 2009. Around 3.5 teaspoons of HPN-100 delivers the same amount of active ingredient as the maximum dose of forty Buphenyl tablets.

The phase III trial will assess blood ammonia concentrations after four weeks in UCD patients to investigate non-inferiority of HPN-100 to Buphenyl. The drug has orphan status for UCD, as well as for hepatic encephalopathy in patients with cirrhosis for which a phase II trial is ongoing in the US and Eastern Europe.

Returning to anti-cancer drugs, ImClone, a subsidiary of Eli Lilly, is developing **necitumumab**, a fully-human monoclonal antibody against EGF receptors, the upregulation of which is implicated in lung cancer. In November 2009 a phase III trial of necitumumab for non-small cell lung cancer (NSCLC) was started in Europe. NSCLC is relatively insensitive to standard chemotherapy and the trial is comparing the safety and efficiency of necitumumab in combination with the standard treatment pemetrexed and cisplatin with pemetrexed and cisplatin alone.

The drug is also being investigated for treatment-naive metastatic or locally advanced colorectal cancer in Europe.

Nabi Biopharmaceuticals meanwhile is developing **NicVax™** (formerly known as Nabi-NicVAX) as a candidate for the prevention and treatment of nicotine addiction. Comprising a nicotine hapten bound to a carrier protein, the injectable vaccine was found in phase II trials to stimulate the production of antibodies against nicotine that prevent its entry into the brain. The first of two planned phase III trials began in November 2009, with results expected in September 2011.

The double-blind, placebo controlled trial will see 1,000 patients receive monthly doses of vaccine for six months. The primary endpoint will be the rate of cigarette abstinence at 12 months, with other endpoints including NicVAX's effect on withdrawal symptoms, cigarette consumption and cigarette dependency. Nabi Pharmaceuticals is seeking a partner to develop and commercialize NicVAX.

Our last drug entering phase III trials is AVEO Pharmaceuticals's **tivozanib**, a tyrosine kinase inhibitor for the potential oral treatment of solid tumors. Tivozanib is a quinolone urea-derived inhibitor of vascular endothelial growth factor, critical for producing new blood vessels in tumors.

Buoyed by positive phase II trial results, AVEO began a phase III trial in December 2009 comparing tivozanib with sorafenib (Nexavar™), currently approved for first-line use in patients unsuitable for the historical standard of care, immunotherapy. 500 Patients with advanced RCC will be assessed for progression-free survival over 24 months.

The drug is also undergoing phase I/II trials stage for breast, colorectal and gastrointestinal cancers, and NSCLC. Japanese licensee Kyowa Hakko Kirin also began a phase I trial for hepatocellular carcinoma in Japan in September 2009.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE II TRIALS

| DRUG | DISEASE | COMPANY |
|-------------------------------------|-----------------------------|---------------------------------------|
| ALKS-33 | Alcohol addiction | Alkermes |
| recombinant PEG-interferon lambda-1 | Hepatitis C virus infection | ZymoGenetics/ Bristol-Myers Squibb |
| PHA-848125 | Thymic cancer | Nerviano Medical Sciences |
| PCI-27483 | Pancreatic cancer | Pharmacyclics |
| SBI-087 | Rheumatoid arthritis | Pfizer |

We start our crop of drugs entering phase II trials with ALKS-33, an orally administered opioid receptor modulator for the treatment of alcohol addiction. A phase II trial for alcoholic dependency began in November 2009.

Developed by Alkermes under license from Rensselaer Polytechnic Institute, [ALKS-33](#) has advantages over existing oral therapies because it is not metabolized by the liver. The 440-patient phase II study, ALK33-005, will assess three doses of the drug and should be completed in October 2011. It follows the successful ALK33-003 and ALK33-004 phase I trials in which ALKS-33 was active within 15 minutes of administration, demonstrated blood plasma levels indicating suitability for daily dosing, and blocked the effects of the opioid agonist remifentanyl for 24 hours.

The main reason for liver transplantation in the US is hepatitis C virus (HCV) infection, which accounts for around 20,000 deaths a year. The current standard of treatment for HCV infection is weekly injections of PEGylated interferon alfa (PEG IFN-alfa) for 48 weeks along with oral ribavirin. But the side effects of the treatment can lead to discontinuation, and just half of patients respond to treatment.

A subcutaneous formulation of [recombinant PEG-interferon lambda-1](#) from Zymogenetics and Bristol Myers Squibb may meet some of this treatment need. A phase II study began in October 2009 comparing PEG IFN-lambda plus ribavirin with standard interferon therapy in treatment-naive patients. At the time the study was intended to be complete in March 2012. The companies hope the new regimen will result in fewer side effects

because PEG IFN-lambda activates the same antiviral signaling pathway as PEG IFN-alfa but through a distinct receptor present on fewer cells, and at lower levels on the hematopoietic cells that are affected by PEG IFN-alfa. This is supported by phase I trials in both relapsed and treatment-naive HCV patients.

There is no standard approved treatment at all for thymic cancer. Nerviano Medical Sciences is developing [PHA-848125](#), a multiple cyclin dependent kinase and TRKA inhibitor for potential oral treatment of advanced and/or metastatic tumors. In a phase I dose escalation study in 22 patients, six demonstrated stable disease, with two maintaining this for more than 3 months. A phase II trial in a planned 60 thymic carcinoma patients began in December 2009 based on a recommended phase I dose of 150 mg/kg.

Staying with cancer, a phase II trial in pancreatic cancer of Pharmacyclics' [PCI-27483](#) began in November 2009 in the US. Many types of cancer, including lung, breast, colorectal, gastric and 90% of pancreatic cancers, express high levels of the surface protein tissue factor (TF) on their cells. The blood protein Factor VIIa binds to TF, resulting in the Factor VIIa:TF complex which has been implicated in the progression of solid tumors and the thromboembolic complications that are a leading cause of death in cancer patients. Pharmacyclics hopes that the drug will work on two levels: by inhibiting tumor growth and decreasing the incidence of thromboembolic events.

PCI-27483 has also been investigated in other indications caused by blood clots, such as deep vein thrombosis. Pharmacyclics licensed the program from Celera following its exit from drug discovery in 2006, and in turn is now looking to outlicense the drug.

Last in our selection of recent phase II entrants is [SBI-087](#) (PF-5230895) from Pfizer, an injectable, CD20-directed immunopharmaceutical indicated for the treatment of rheumatoid arthritis (RA). Pfizer gained the drug as part of its Wyeth acquisition in October 2009, and the following month announced the initiation of a US-based phase II trial. Four dosing schedules of SBI-087 will be compared with placebo for ACR 20 response in 200 patients with active RA on a stable dose of methotrexate.

The drug is also being investigated for multiple sclerosis, and systemic lupus erythematosus for which phase I trials are ongoing.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE I TRIALS

| DRUG | DISEASE | COMPANY |
|-------------------------|--------------------------------------|--|
| Ad4-H5-Vtn | Avian influenza | PaxVax |
| adoptive T-cell therapy | HIV infection | Adaptimmune |
| BI-505 | Multiple myeloma | BioInvent International |
| CHF-5074 | Alzheimer's disease | Chiesi |
| sFLT-01 | Wet age-related macular degeneration | Applied Genetic Technologies / Genzyme |

Our first candidate entering trials this quarter is [Ad4-H5-Vtn](#), an oral avian influenza vaccine from PaxVax. A phase I safety and immunogenicity trial was started in healthy volunteers in the United States in October 2009 and was expected to be complete by October 2010. The vaccine delivers the gene for H5 hemagglutinin in an enteric-coated capsule formulation to prevent it being broken down in the intestinal tract. An oral vaccine could revolutionize influenza vaccination – an area whose importance was highlighted by the recent H1N1 swine flu threat.

Moving to HIV infection, Adaptimmune – a spin-off from MediGene AG - is developing an [adoptive T-cell therapy](#) for the potential treatment of HIV infection. The immune system normally targets viruses using specific receptors on T-cells, but one of the reasons HIV is such a difficult foe is its ability to constantly mutate and escape detection by these receptors. Adaptimmune has engineered T-cell receptors that recognize a range of HIV mutants and trigger a potent immune response when transferred into a patient's own T-cells.

In a trial that started in the US in October 2009, HIV-infected patients with well-controlled disease will receive a single dose of their own T-cells modified to contain either the wild-type T-cell receptor for a particular HIV mutant or a higher-affinity version engineered to recognize and remove HIV. The trial will assess whether the modified cells are safe and at what doses they can be given.

With a phase I trial in advanced multiple myeloma (MM) patients which began in December 2009, BioInvent International is building on positive preclinical data with its ICAM-1 antibody and apoptosis inducer [BI-505](#) which saw the drug match current standard bortezomib.

The trial of 30-40 patients will determine the optimal dose for later phase II trials along with safety, pharmacokinetics and pharmacodynamics of once-weekly intravenous infusions every other week for four weeks. In December 2007 BioInvent announced plans to first investigate BI-505 in blood cancers before moving on to solid tumors and the drug now has orphan status for MM in both the US and Europe.

Healthy US male volunteers will be given [CHF-5074](#), Chiesi's candidate treatment for Alzheimer's disease, in a phase I trial which began in October 2009. The drug is a capsule formulation of a flurbiprofen analog and gamma secretase inhibitor which inhibits the release of the beta-amyloid 1-42 that makes up the disease-causing plaques found in the brains of Alzheimer's patients. Studies in mice overexpressing amyloid precursor protein have shown that CHF-5074 can improve both contextual and spatial memory. The need for an effective Alzheimer's treatment is huge. There is no way to prevent or halt the disease, with only around half of patients responding to existing drugs, and then only in the early stages.

And finally, Applied Genetic Technologies has teamed up with Genzyme to develop a candidate gene therapy for wet age-related macular degeneration. A leading cause of blindness, the disease sees fragile new blood vessels behind the retina start to grow under the macula, leaking fluid and scarring it, leading to sight loss.

The therapy comprises an adeno-associated virus vector carrying a gene encoding [sFLT-01](#), a soluble form of the vascular endothelial growth factor receptor that suppresses VEGF and prevents blood vessel formation.

Preclinical data have demonstrated the ability of sFLT-01 to inhibit experimentally-induced neovascularization in non-human primates for up to 5 months after administration. The phase I trial, which started in December 2009 in a planned 34 wet AMD patients will test the safety and tolerability of a single intravitreal injection.

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Sue Besaw

Phone: +1 215 823 1840

Email: susan.besaw@thomsonreuters.com

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Philadelphia +1 800 336 4474
+1 215 386 0100

Europe, Middle East and Africa

London +44 20 7433 4000

Asia Pacific

Singapore +65 6411 6888
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